CONFIDENTIAL

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"Electrocardiographic Effects of Nicotine in the Rabbit with Experimental Coronary Atherosclerosis"

I. Methodology

1. Animal care

In the interim report, problems dealing with animal care were discussed. We had concluded that the Dutch belted rabbit on the cholesterol diet seemed to survive longer than the albino rabbit. This consideration is of paramount importance since it takes a long time for coronary atherosclerosis to develop. We noted, however, that in the first weeks on the experimental diet the animals are apt to develop a fatal infectious illness.

The following change was therefore made in procedure: On arrival from the farm, all animals are put on a stock diet for 10 days and given Sulmet (Lederle sulfamethylthiazole) intraperitoneally every other day for 3 injections, each 200 mg. total. At the end of 10 days, the animals are continued on the stock diet if in the control group, or shifted to the cholesterol diet. We still employ a cholesterol diet containing 2% cholesterol and 6% corn oil.

II. Results of Electrocardiographic Studies in the Intact Animal

1. Control Animals

In 27 tests done on different days on normal rabbits under Nembutal anesthesia (20 mg./Kg., i.v.), nicotine in doses of 0.1, 0.25, 0.5 and 1.0 mg./Kg. intravenously produced no change in the electrocardiogram which might be regarded as indicative of an effect on the coronary circulation, when observed for periods of 10 to 15 minutes after injection of the drug.

2. Cholesterol-fed Animals

Since the atherosclerotic rabbits with positive ergonovine tests were sick animals, and their survival for coronary perfusion was desired, the intravenous dose of nicotine in this group was reduced to 0.05 mg./Kg. This is still large in terms of the level of nicotine in the blood stream after smoking.

In 9 cholesterol-fed animals with a positive ergonovine test (Table I), the intravenous injection of this dose of nicotine bitartrate (0.05 mg/Kg.) produced electrocardiographic changes clearly indicative of coronary insufficiency in one animal, namely, an S-T segment depression of 0.5 mm. (Table 1, M_6). Microscopic examination of the coronary arteries in 8 of these animals showed atherosclerosis; one section is not yet available for study.

The effect of nicotine on the rate of these atherosclerotic hearts is also indicated in Table 1. From the average control rate of 248 beats/min., the rate at the end of 10 minutes had dropped to 229 beats/min. On the average, a fall in rate began within one minute after nicotine injection. Two animals showed an initial acceleration of heart rate.

III. Results of Perfusion Studies of the Isolated Rabbit Heart.

The effect of nicotine bitartrate on the amplitude and rate of contraction and on the coronary flow in the isolated preparation of the atherosclerotic heart (following a positive ergonovine test) was studied in 10 hearts with a dose of 0.05 mg., and in 8 hearts with a dose of 0.1 mg. With the smaller dose of nicotine, the maximal change in amplitude expressed in per cent of the control level, was /24.5%; for heart rate, it was -5.8%; and for coronary flow it was -1.4%. With the larger dose of nicotine, similarly the average percentage change in amplitude from the control level was /53.6%; for heart rate, it was -2.6% and for coronary flow -19.5%. Thus, nicotine in a relatively large dose increases the amplitude of contraction, has little effect on heart rate, and may significantly reduce coronary flow. More observations are needed on the individual variability of this effect on coronary flow, which is not uniform.

Additional perfusion experiments will have to be done before it can be stated whether normal and atherosclerotic hearts react similarly to nicotine with respect to these different structures: myocardium, arterial musculature, and the pacemaker and conduction system.

TABLE I

Effect of Intravenous Nicotine Bitartrate (0.05 mg./Kg.) on the Electrocardiogram in 9 Cholesterol-Fed Rabbits with Positive Ergonovine Tests (Nembutal Anesthesia).

Rabbit No.	Control Heart Rate	Heart rate-minutes after injection ¼	1	5	10	E.C.G. changes after nicotine	Coronary Arteries
M_5	248	144	130	172	180	T-wave (lead II) from upright to diphasic	Plaques
M_6	300	300	300	284	264	S-T segment depressed 0.5 mm.	Foam cells
P_1	210	212	209	205	201	T-wave (lead II) inverted; decreased amplitude of T-wave (V_4) from 4 to 2 mm.	Plaques
P_2	170	240	175	170	162	None	Plaques
Q_2	260	254	245	259	250	None	Plaques
Q_7	245	300	285	275	250	None	Plaques
Q_9	225	215	210	210	205	None	Plaques
M_1	248	246	240	240	240	None	Plaques
U_9	323	305	320	320	310	Decreased amplitude of R-wave in (V4)	-
Averages	248	247	235	237	229		

TABLE 2

Effects of Nicotine (0.05 and 0.1 mg.) on the Perfused Atherosclerotic Rabbit Heart

No.of Hearts	AMPLITUDE OF CONTRACTION				HEART RATE				CORONARY FLOW			
	Ringer-Locke mm.	% change	Nicotine mm.	% change	Ringer-Locke beats/min.	% change	Nicotine beats/min.	% change	Ringer-Locke cc./min.	% change	Nicotine cc./min.	% change
					Nicotine 0.05 mg.							
10	17.0	-1.1	7.0	∕ 24.5	108	-0.9	105	-5.8	19.9	-4.7	14.4	-1.4
					Nicotine 0.1 mg.							
8	17.1	-1.7	7.1	∕ 53.6	106	-1.6	119	∕2.6	19.8	-3.9	14.0	-19.5